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Environmental Tobacco Smoke Exposure and Occupational Heart Disease

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In 1991, the Occupational Safety and Health Administration (1) requested information on exposures and potential adverse health effects that may be associated with poor indoor air quality in the work environment, including information on exposure to environmental tobacco smoke (ETS). One review article, which focused on heart disease and which was published prior to the agency's request, concluded as follows: "the combination of epidemiological studies with demonstration of physiological changes with exposure to ETS, together with biochemical evidence that elements of ETS have significant adverse effects on the cardiovascular system, leads to the conclusion that ETS causes heart disease" (2). Others, however, have expressed conflicting interpretations of human and animal studies on ETS, concluding that it has not been scientifically demonstrated that ETS exposure increases the risk of heart disease in nonsmokers (3,4). The ongoing debate should not only consider the claimed association between ETS work exposure and heart disease in particular, but also occupational heart disease in general. The primary purpose of this chapter is to review the toxicological basis for identifying chemical substances that may be associated with heart disease in the workplace.

At the outset, it should be emphasized that proof of an association between ETS workplace exposure and heart disease is a complex process. Workers, such as garage attendants, may be exposed to one or more substances (such as carbon monoxide) found both in ETS and in other sources, so the total exposure is the sum of two or more sources, for example, vehicular emissions, ambient air pollution, and ETS. The same group of workers may have varied personal habits that have been reported to be associated with heart disease, such as consumption of cholesterol and fats and xanthine beverages at the employee's cafeteria, physical inactivity on the job, and job-related stress. Outside the workplace, there are additional potential risk factors for heart disease, such as lack of leisure time exercise, dietary cook-

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ing fat and salt content, household exposure to cooking gas, gas heaters, and household solvents. Other major risk factors reported for heart disease include the worker's familial history of heart disease, diabetes, hypertension, hyperlipidemia, and obesity. Any conclusion on a possible role of ETS in heart disease necessitates controlling for such risk factors.

INVESTIGATIVE METHODS FOR INDUSTRIAL CHEMICALS

Although there are over 300 potentially hazardous chemicals in the workplace, there are less than three scores of industrial chemicals that have been suggested to be associated with heart disease such as ischemic heart disease, coronary atherosclerosis, and cardiac arrhythmia and cardiomyopathy. Although heart disease is the leading cause of death in the United States, occupational exposure to chemicals is considered less prevalent and less important than risk factors in the diet, in the environment, and in familial or inherited susceptibility to cardiovascular diseases.

Although it is relatively simple to establish a strong association between exposure to halogenated solvents and cardiac arrhythmias, it is more complex to obtain supportive evidence as to whether chemicals play a major role in coronary ischemic heart disease and atherosclerosis. Occupational heart diseases can be grouped into three major categories. These can be subgrouped according to the method of investigation, which may involve clinical studies, pathological observations, or experimental animal studies (Table 1): (a) *ischemic heart disease* (Methods A, B, and C), including mortality studies, exercise testing for angina pectoris, and coronary blood flow indicators; (b) *coronary atherosclerosis* (Methods D, E, and F), demonstrable in patients by angiography and histopathology, atherosclerosis in experimental animals, and *in vitro* studies of hematologic factors; and (c) *cardiac arrhythmia and myopathy* (Methods G and H), both clinically and experimentally induced. The three groups of methods and eight subgroupings (A to H) are carried over to consideration of occupational heart disease associated with exposure to chemicals in the course of manufacturing and processing of industrial products. The chemicals supposedly associated with occupational heart diseases are listed in Table 1 under five classes: one inorganic and four organics. Each compound is identified by notations on investigative methods A to H.

Inorganic Oxides and Metals

Carbon monoxide is most widely discussed as a major substance in the etiology of occupational heart disease. Workplace exposure to carbon monoxide is encountered when it is generated in manufacturing an industrial product. In the steel industry, carbon monoxide is produced in blast furnace

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TABLE 1. *Industrial chemicals reported to be associated with occupational heart disease*

Industrial chemicals	Ischemic heart disease	Coronary atherosclerosis	Arrythmias and myopathy
Inorganics: oxides and metals			
Carbon monoxide[a]	A B C	D E F	G H
Carbon dioxide[a]			G
Nitrogen oxides[a]			G
Arsenic	A		H
Cadmium[a]	A		
Cobalt	A		H
Lead	A	F	
Nitrogenous compounds			
Nicotine[a]	A		
Aniline[a]		F	
Catechol[a]			G
Dinitrotoluene	A		
Ethylene glycol dinitrate	A C		G
Hydrazine[a]			G
Hydrocyanic acid[a]	C		H
Nitroglycerin	A C		G
Pyridine[a]			G
2-Toluidine[a]		F	
Polynuclear aromatic hydrocarbons	A		
Benzo[a]pyrene[a]		E	
7,12-Dimethyl (*a,h*) anthracene		E	
3-Methylcholanthrene		E	
Nonhalogenated solvents			
Carbon disulfide[a,b]	A B C	D E	H
Acetaldehyde[a]			G
Acetone[a]			G
Benzene[a]			G
Dimethylamine[a]			G
Methylamine[a]			G
Phenol[a]			G H
Toluene[a]			G
Halogenated solvents			
Methyl chloride[a]			G H
Methyl chloroform			G H
Methylene chloride		F	G H
Trichlorofluoromethane			G H

[a]Sidestream smoke (SSS) constituent.

[b]Metabolite carbonyl sulfide is ETS constituent.

Method A, mortality studies; Method B, exercise testing and angina pectoris; Method C, coronary blood flow indicators; Method D, coronary angiography and histopathology; Method E, atherosclerosis in experimental animals; Method F, *in vitro* hematologic factors; Method G, irregular heartbeat; Method H, experimentally induced cardiomyopathy.

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smelting of iron ore, cast welding, and vehicular production. Operators of vehicles, parking attendants, tunnel workers, car emission inspectors, tool operators, and traffic police are constantly exposed to exhaust fumes and elevated levels of carboxyhemoglobin in such workers have been reported. All eight subgroups of methods have been applied to arrive at an extensive cardiac toxicologic profile of carbon monoxide (Methods A to H in Table 1). The two other oxides and four heavy metals listed in Table 1 have been less thoroughly investigated.

Among heavy metals reportedly associated with heart disease are arsenic, cadmium, cobalt, and lead. The pathogenesis of heart disease potentially associated with workplace exposure may vary according to volatility of the metallic compound and its exposure level. Cadmium has not been reported to influence the heart directly but may be related to hypertension, which may lead to cardiac complications. Lead may influence the blood and ultimately interfere with cardiac metabolism and function. Arsenic, cobalt, and lead are cellular poisons and there are experimental heart models to support the occurrence of cardiomyopathy from these metals. Only cadmium has been detected in tobacco leaf and tobacco smoke; traces of cadmium are derived from soil.

Nitrogenous Compounds

The ten examples in this group include the following: nicotine (an alkaloid), hydrocyanic acid, and raw products for the manufacture of explosives such as ethylene glycol dinitrate and nitroglycerin. The other six examples (aniline, catechol, dinitrotoluene, hydrazine, pyridine, 2-toluidine) are necessary in the manufacture of pharmaceuticals, pesticides, and dyes. The cardiac toxicologic profiles for each of these compounds are not completely known and have been studied only by one, two, or three methods. The entry on nicotine refers to handling of tobacco leaf, such as cigar manufacturers, kiln dryers, and warehouse operators.

Polynuclear Aromatic Hydrocarbons (PAH)

These are formed as a result of pyrolysis or incomplete combustion of organic materials. There are several hundred PAHs and only a dozen have been reported to be associated with skin tumors via skin painting in mice. Benzo[*a*]pyrene is the most widely studied compound and only research scientists are occupationally exposed to this single PAH. Workers potentially exposed to PAH mixtures include coke oven operators, creosote wood applicators, asphalt road pavers and roofers, aluminum smelters, and diesel engine operators. Benzo[*a*]pyrene and two other PAHs listed in Table 1 have

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been reported to be associated with atherosclerosis in an experimental model. There are no human studies relating to heart disease other than mortality statistics of workers exposed to PAH mixtures.

Nonhalogenated Solvents

Carbon disulfide is a solvent used in the manufacture of viscose rayon, cellophane film, electronic vacuum tubes, sulfur-containing soil disinfectants, and carbon tetrachloride. This is the only solvent for which there are strong data on an association with ischemic heart disease in workers, as well as coronary atherosclerosis in experimental animals. The cardiac toxicologic profile is complete except for the lack of *in vitro* studies on hematologic factors and cardiac susceptibility to arrhythmia. The seven other solvents have not been studied for occurrence of ischemic heart disease and coronary artherosclerosis.

Halogenated Solvents

The author and his colleagues have written monographs on the cardiotoxicity of chlorinated and fluorinated solvents (5–7). Four solvents are identified in Table 1 from the original list of more than 100 solvents that are considered cardiotoxic. The four selected solvents (methyl chloride, methyl chloroform, methylene chloride, and trichlorofluoromethane) are reported to cause fatal cardiac arrhythmia and sudden death in the course of accidental industrial poisonings. Usually it cannot be proved whether cardiac arrest was caused by a direct cardiac effect or the result of respiratory paralysis and coma, since most halogenated solvents are not only cardiotoxic but also central nervous system depressants. Experimental animal studies have supported the potential role of sublethal doses of solvents in cardiac arrhythmias and myopathies, independently of coronary vessels and central nervous system involvement.

Miscellaneous Compounds

Industrial chemicals potentially related to heart disease, but which appear not to directly influence the heart, blood vessels, and circulating blood, are omitted from Table 1. Insecticides, including organophosphates, are reportedly associated with irregular heart rhythms because of their influence on the autonomic nervous system. Chronic obstructive lung disease associated with inorganic dust particles can cause cor pulmonale. Exposure to nephrotoxins, such as mercury and dyes, has been reported to lead to cardiac complications, including congestive heart failure.

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CONSTITUENTS OF ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke is a diluted and aged mixture of constituents derived from either the burning end or cigarette butt: mainstream smoke inhaled from the filtered or unfiltered tip; and sidestream smoke from the lighted end. Nonsmokers sharing a workroom with smoking workers may be exposed to ETS. Sidestream smoke is not inhaled directly by nonsmokers but is diluted immediately by air in the workplace and continuously by air exchanges. The magnitudes of differences between concentrations of substances in mainstream smoke inhaled by the smoker and ETS exposure of nonsmokers have been summarized in a National Research Council monograph (8). The ranges reported in the literature (parts per million or parts per billion) are as follows:

	Mainstream Smoke	ETS
Carbon monoxide	24,900–57,400 ppm	1–18.5 ppm
Nicotine	430,000–1,080,000 ppb	0.5–7.5 ppb
Benzo[*a*]pyrene	5–11 ppb	0.0001–0.074 ppb

The dilution factors for peak values are as follows: 3100 for carbon monoxide, 144,000 for nicotine, and 148 for benzo[*a*]pyrene. There is no uniform dilution for all three because of varied levels in mainstream smoke relative to sidestream smoke. The unpredictable fates of vapor components (e.g., carbon monoxide) and particulates (e.g., nicotine and benzo[*a*]pyrene) are influenced by humidity, temperature, air movement, and adsorption by machinery and furnishings in the workplace.

Work Standards for Industrial Chemicals

The minute levels of carbon monoxide in ETS, up to 3100 times less than the concentration in mainstream smoke, pose a critical challenge to claims that ETS exposure can cause heart disease in nonsmokers. Proponents of the claimed association between ETS exposure and heart disease in general (occupational and nonoccupational) contend that three ETS constituents underlie this relationship: nicotine, carbon monoxide, and polynuclear aromatic hydrocarbons. For completeness, there are 21 reported constituents of sidestream smoke that are also used as industrial chemicals, which are sometimes discussed as potentially associated with heart disease. These are the same 21 industrial chemicals listed in the first column of Table 1 that are manufactured, processed, or emitted in workplaces and are potentially associated with heart disease (marked with superscript *a* in first

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column, Table 1). Most halogenated solvents, heavy metals, and polycyclic aromatic hydrocarbons have not been detected in ETS (no superscript in Table 1).

The list of 21 sidestream smoke constituents inputed to ETS in Table 2 is a revision of the author's listing of suspected pulmonary carcinogens in ETS (9,10). Also listed in Table 2 are corresponding threshold limit values (TLVs) for various substances, defined as the recommended standards for 8-hr daily exposure for the prevention of occupational disease (11). Table 2 includes a column of target organs for acute or initial exposure, as well as for chronic or long-term exposure. When TLV levels are exceeded, early and late signs of toxicity appear in skin, mucosa, lungs, liver, kidneys, blood, blood vessels, and nervous system. Manifestations of cardiotoxicity may occur either in acute lethal concentrations (more than 20 times TLV) or repeated exposure to very high, but sublethal, concentrations (more than two to five times TLV, depending on the compound).

TABLE 2. *Sidestream smoke* (SSS) *constituents with threshold limit values (TLV)*

Chemical name	Acute/chronic[a]	Max SSS (mg cig)	TLV (mg/m^3)	Cigarette equivalent
Nicotine	M/N	8.2	0.5	6.6
Carbon monoxide	B/N	108	55	50
Methyl chloride	M/N	0.88	10.3	1,170
Cadmium	M/P	0.0007	0.01	1,430
Acetaldehyde	M/P	1.26	180	1,430
Nitrogen oxides	M/N	2.8	50	1,780
Carbon dioxide	N/N	440	9000	2,040
Pyridine	M/H	0.39	16	4,100
Phenol	M/P	0.25	19	7,600
Hydrocyanic acid	B/N	0.11	11	10,000
Methylamine	M/N	0.1	13	13,000
Benzene	N/B	0.24	32	13,300
Catechol	D/K	0.14	23	16,500
Aniline	B/B	0.011	8	44,000
Dimethylamine	M/H	0.036	18	50,000
Carbonyl sulfide	N/V	0.0546	30*b*	54,945
Hydrazine	M/H	0.00009	0.13	145,000
Acetone	M/N	1	1780	178,000
Benzo[*a*]pyrene	*c*	0.00009	0.2	222,000
2-Toluidine	M/B	0.003	9	300,000
Toluene	N/B	0.000035	375	1,000,000

[a]Target organs: B, blood; D, dermal; H, hepatic; K, kidney; M, mucosal; N, nervous; P, pulmonary; V, vascular.

[b]Metabolite of carbon disulfide with corresponding TLV used to calculate cigarette equivalent.

[c]No TLV for benzo[*a*]pyrene; TLV for coal tar pitch volatiles used to calculate cigarette equivalent.

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Cigarette Equivalents to Attain TLV

The 21 sidestream smoke constituents with established workplace standards are listed in the order of increasing number of cigarette equivalents, defined as the number of cigarettes burned in a sealed enclosure of 100 m^3 to attain, but not to exceed, the corresponding TLV (last column, Table 2). The list starts with nicotine, which is a reported mucosal irritant (acute exposure) and an autonomic nervous system stimulant (chronic or repeated exposure). The maximum reported sidestream smoke (SSS) collected from one burning cigarette is 8.2 mg. On the basis of TLV (0.5 mg/m^3), it would take 6.6 cigarettes to attain TLV for 100 m^3 in a sealed, unventilated enclosure ($0.5 \times 100 \div 8.2$). It is unlikely for the nicotine concentration in public places to attain the TLV level. If smoking has been at an extremely high level in poorly ventilated rooms, subjective discomforts would be expected to lead to corrective measures before nicotine levels would approach the TLV. The second SSS constituent listed in the order of increasing cigarette equivalents is carbon monoxide: 50 cigarettes burning in a 100 m^3 sealed chamber to attain the corresponding TLV (12).

Other than nicotine and carbon monoxide, the remaining 19 SSS constituents would require more than 1000 cigarettes to attain the corresponding TLV. Such excessively high cigarette equivalents suggest that to attain TLV levels, more than 1000 cigarettes need to be ignited simultaneously in an enclosed space of 100 m^3. Consideration of cigarette equivalents clearly indicates that exposure to ETS constituents in workplaces rarely approximates TLVs.

Nicotine as ETS Marker

That nicotine and its major metabolite (cotinine) are detected in blood and urine of ETS-exposed nonsmokers has been utilized by proponents of the ETS–heart disease hypothesis. Their reasoning is as follows: since nicotine is the major cause of heart disease seen in cigarette smokers, it follows that any nicotine derived from ETS can cause heart disease in exposed nonsmokers. However, there is disagreement concerning whether any nicotine absorbed by nonsmokers can influence the heart. The estimates of ETS exposure are as follows: a nonsmoker's exposure might be, at most, the nicotine equivalent of 1/100 to 1/1000 cigarette in one hr, which has not been reported to have a significant pharmacologic action. In animal experiments, inhalation, ingestion, parenteral injection, and dermal application of nicotine have been reported to influence cardiac function, coronary circulation, and atherogenesis, but these studies used amounts of nicotine that cannot be attained by ETS exposure. Furthermore, coronary atherosclerosis has not been reproduced in experimental animals by injection of nicotine. High nicotine levels of pipe smokers compared to cigarette smokers are not report-

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edly associated with an increased incidence of ischemic heart disease (13). Workers processing tobacco leaf (cigar making, leaf curing, and warehouse workers) also have not been reported to show a higher incidence of heart disease, compared to nontobacco workers (14).

Cardiac Toxicologic Profile of Industrial Chemicals

The 21 chemicals listed in Table 2, when individually used in factories below the corresponding TLV, have not been associated with heart disease nor any adverse effect on corresponding target organs, that is, mucosal surfaces, skin, blood, nervous system, lungs, kidneys, and liver (see second column of Table 2). The same 21 ETS constituents also appear in Table 1 of industrial chemicals, together with 11 industrial chemicals *not* reported to be present in ETS. As outlined in Table 1, the existing methods for establishing cardiac toxicologic profiles are as follows: Methods A, B, and C for ischemic heart disease; Methods D, E, and F for coronary atherosclerosis; and Methods G and H for cardiac arrhythmia and myopathy. Most industrial chemicals have been studied by one or two methods, thus contributing to an uncertainty of whether these 21 chemicals are related to heart disease. Those that have been studied by three to eight methods have a stronger basis for claims of a relationship with occupational heart disease, namely, carbon monoxide, ethylene glycol dinitrate, nitroglycerin, carbon disulfide, and methylene chloride. There are review articles on industrial chemicals reportedly associated with heart disease (15–17).

A principal objective of this chapter is to evaluate the potential relationships between occupational chemicals and heart disease, in terms of the extent of the available data from human studies and animal experiments. There are reviews on individual industrial chemicals and the occurrence of diseases not limited to the heart (11,18,19). A standard source of reference is the Registry for Toxic Effects of Chemical Substances available in hard copy (20) as well as on-line in the TOXNET database updated by the National Library of Medicine and National Institute of Occupational Safety and Health. Textbooks on internal medicine and cardiology do not have special chapters devoted to occupational heart diseases so that it has been difficult to interest the medical profession. Because industrial chemicals are potentially associated with heart disease by the inhalational route, a World Health Organization monograph entitled *Air Quality Guidelines for Europe* (21) is a helpful reference source. It discusses the following industrial chemicals in a uniform format: inorganic oxides such as carbon monoxide and nitrogen dioxide; heavy metals such as arsenic, cadmium, and lead; polynuclear aromatic hydrocarbons such as benzo[*a*]pyrene; nonhalogenated solvents such as benzene, carbon disulfide, and toluene; and halogenated solvents such as methyl chloroform and methylene chloride. These 11 industrial chemicals identify those that have been measured indoors (workplace envi-

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ronment) but also emitted outdoors into the environment. Ischemic heart disease is mentioned under carbon monoxide and carbon disulfide.

ISCHEMIC HEART DISEASE

Ischemic heart disease is represented clinically by angina pectoris, myocardial infarction, cardiac arrhythmia, cardiogenic shock, and sudden death. The epidemiologic and clinical literature on work-associated ischemic heart disease consists of the following: Method A, mortality statistics; Method B, exercise testing for anginal pain; and Method C, coronary blood flow indicators. The plan is to state how each method has been applied to the concept that ischemic heart disease is related to exposure to chemical substances in the manufacture of industrial products. Although ETS levels are unlikely to attain their corresponding TLV, it is important to discuss the existing claim that the mere presence of these chemicals is sufficient to suggest an association between ETS and occupational heart disease.

Method A: Mortality Studies

There are scant data on heart disease in workers differentiated by exposure or nonexposure to ETS in the workplace. Most published studies relate to differences in spousal smoking habits, based on the premise that mortality rates of nonsmokers might be influenced by smoking habits of their spouses. In 1984, Schievelbein and Richter (22) reviewed the available literature and concluded that in concentrations of carbon monoxide and nicotine reportedly present in ETS, it is unlikely for ETS exposure to play any role in the development and progression of ischemic heart disease. The 1986 Reports of the Surgeon General and the National Research Council, after examining the available information, concluded that further studies on the potential relationship between ETS exposure and cardiovascular disease are needed in order to determine whether ETS increases the risk of cardiovascular disease in general, and of ischemic heart disease in particular (8,23). Recent epidemiologic studies were reviewed by Wexler (4), who questioned the reported relationship between household exposure to ETS and heart disease.

Prospective (cohort) and retrospective (case control) studies have been conducted on the potential relationship between ETS exposure and IHD incidence. Although some spousal studies (smoker married to nonsmoker) report a statistically significant association, most studies do not. Lee and his collaborators (24) conducted studies in England consisting of administering a questionnaire to 200 hospital patients and 200 controls for each gender and age group. Patients with ischemic heart disease and controls did not show any statistically significant difference in ETS exposure based on smoking habits of spouses. Exposure to ETS was also evaluated by an index of pres-

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ence in the workplace, during travel, and at leisure. From the standpoint of worker ETS exposure, the negative results of Lee et al. (24) are more relevant than positive results of spousal studies that do not include ETS exposure outside the home environment.

Carbon Monoxide

Heart disease mortality rates have been reported for workers exposed to high levels of carbon monoxide from vehicular emissions (tunnel workers, bus drivers, parking attendants) and industrial furnaces (steel foundry, coke oven, chemical manufacture) (25,26). However, the results of occupational exposure to high levels of carbon monoxide do not support the argument that this substance contributes to heart disease associated with ETS exposure, in which reported levels of the gas are a tiny fraction of the TLV.

Carbon Disulfide/Carbonyl Sulfide

These two compounds are linked by the fact that the former is an industrial chemical reported to be associated with heart disease among workers producing viscose rayon fibers. This compound is metabolized to carbonyl sulfide, which happens to be a reported SSS constituent. The concentration of carbonyl sulfide is so low that it is unlikely to attain the TLV (Table 2: 54,945 cigarettes to attain TLV). However, it is important to discuss mortality studies of rayon viscose workers, because other than carbon monoxide, carbon disulfide is the only industrial chemical for which there are extensive data on an association with ischemic heart disease. In a critical review of the toxicologic literature on carbon disulfide, Beauchamp et al. (27) reviewed data on the mortality rates of viscose rayon workers. In Finland, where there is a high incidence of ischemic heart disease, a significantly higher mortality rate has been reported among exposed workers compared to a control group. However, in Japan where there is a notably lower incidence of ischemic heart disease, no increased mortality rate has been reported among viscose rayon workers. The excess deaths attributed to carbon disulfide became apparent if predisposing risk factors existed, such as hypertension, hyperlipidemia, and excessive intake of cholesterol and saturated fats (27,28).

The above observations are essential to consider in attempts to interpret mortality studies on ETS exposure. Dietary intakes of cholesterol and fatty food were not considered as a confounding factor in mortality studies relating to workers exposed to the industrial chemicals listed in Table 1 (with Method A notation). The reported higher susceptibility of Scandinavians to heart disease is reflected by the lower TLV (15 mg/m^3) compared to the TLV in other European countries and the United States (30 mg/m^3) (18,19).

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Polycyclic Aromatic Hydrocarbons (PAH)

It has been suggested by proponents of the ETS–heart disease hypothesis that Scandinavian roofers show excess mortality for ischemic heart disease (3). They extrapolate from PAH-exposed roofers to ETS-exposed workers without recognizing the difference in composition of PAH. Exposures to PAH among coke oven workers, creosote wood appliers, and asphalt road builders have not been reported to be associated with excess mortality for heart disease but have been reported to be associated with excess mortality for lung cancer. From the standpoint of chemical composition of PAH exposures determined by nature of product, PAH exposures of roofers are irrelevant to ETS exposure (see also Method F).

Heavy Metals

Mortality studies on work-related exposure have been reviewed by Kristensen (16). Lead and cadmium workers have been reported to show a higher mortality rate from heart disease and hypertension. In the absence of experimental animal studies, heart disease is likely to be a complication of hypertension rather than a direct effect of lead or cadmium on the heart and coronary vessels. The suggestion that heart disease may be associated with workplace exposure to arsenic or cobalt can be traced to instances of beer drinking contaminated with either of these metals, and subsequent death from cardiomyopathy.

Method B: Exercise Testing and Angina Pectoris

Exercise testing is essential for the diagnosis of ischemic heart disease (29). A positive diagnosis is based on the appearance of chest pain or classical angina pectoris after completion of standardized exercise on a treadmill or bicycle ergometer. Exercise testing has also been used to evaluate severity of arteriosclerotic heart disease based on time of onset of an ischemic pattern in the electrocardiogram as well as the appearance of cardiac arrhythmias.

ETS Exposure of Anginal Patients

All available reports on exercise testing do not relate to specific occupational groups comparing two subgroups: with ETS exposure and no ETS exposure. There are two studies on anginal patients that suggested to the investigators that ETS exposure during bicycle ergometry may shorten the time period to onset of chest pain. The first study, reported in 1978, consisted of a group of ten American male veterans (30). For various reasons,

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the 1978 protocol for exercise testing was evaluated by an ad hoc committee of the Environmental Protection Agency. In 1983, the committee concluded that the method used on American male veterans "did not meet a reasonable standard of scientific quality" (31). In 1987, a second study of exercise testing during ETS exposure was reported by Soviet investigators (32). The results were essentially similar to those reported from American veterans. It is this author's opinion that shortening onset of anginal pain during exercise testing as a result of ETS exposure has not been proved pending evaluation of the Soviet protocol. Anti-anginal drugs sold in the United States are supported by results of exercise testing in European laboratories that have been approved by the U.S. Food and Drug Administration and so far, the list does not include any Soviet laboratories.

Influence of Carbon Monoxide on Exercise Testing

Proponents of the theory that ETS exposure aggravates angina pectoris emphasize the presence of carbon monoxide in ETS, in spite of the fact that the concentration inhaled is 3100 times lower than mainstream smoke. Blood carboxyhemoglobin levels of subjects exposed to ETS in public places range from 1 to 3% among nonsmokers. Slight elevations of blood carboxyhemoglobin level (to 2 and 3.9%) have been reported following administration of carbon monoxide in air (100 and 230 mg/m^3) (33). Exercise testing of heart disease patients was reported to result in an ischemic pattern of electrocardiogram at these blood carboxyhemoglobin levels. However, as indicated in Table 2, this would require more than 100 and 200 cigarettes burning in a sealed enclosure of 100 m^3 for carbon monoxide to attain about 2 and 4 times the TLV, respectively.

ETS Exposure as Risk Factor for Angina Pectoris

Proponents of the claim that ETS exposure aggravates angina pectoris have not considered the complexities of the disease separate from other manifestations or complications of ischemic heart disease (i.e., acute myocardial infarction and sudden deaths). Although prospective and retrospective studies report that cigarette smoking is one of many risk factors for acute myocardial infarction and sudden deaths, the data on angina pectoris are even more complex. The 1983 report of the Surgeon General on cardiovascular disease, referring to risk factors, concluded that "variation in the strength of association between smoking and angina pectoris may be influenced by . . . methodological considerations" (ref. 34, p. 70). More recently, it has been argued that the 30-year results of an ongoing prospective study at Framingham, Massachusetts, indicate that cigarette smoking is a negative risk factor in women (i.e., incidence lower in women smokers compared to

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women nonsmokers) (35). The results in men have indicated either a positive or no significant relationship between cigarette smoking and angina pectoris, depending on methodological variation. Some studies relating to cardiac patients admitted to hospitals report that after an initial cardiac episode, the prognosis is not influenced by smoking (36,37). After the initial infarction, prior smoking was not associated with the severity of subsequent complications. These observations on cigarette smoking in relation to the prognosis of myocardial infarction and the influence of angina pectoris raise additional questions. How can ETS, a dilute mixture of tobacco smoke components in air, aggravate angina pectoris or influence the prognosis of acute myocardial infarction, in light of recent inconsistencies in data derived from smokers?

Method C: Coronary Blood Flow Indicators

Coronary arteries visualized by angiography can show obstruction that is organic (arteriosclerosis and thrombosis) or nonorganic (vasospasm) in nature. Total coronary blood flow is measured by a tracer clearance technique. Patients with ischemic heart disease show a reduction in coronary blood flow that is limited to an infarcted area. When infarction is detected in workers previously exposed to carbon monoxide or carbon disulfide, it is not possible to isolate the potential association with chemical exposure from other potentially confounding risk factors. Carbon monoxide alone, by increasing carboxyhemoglobin, can increase coronary blood flow, but the result would be an oversupply of blood without reduced oxygen utilization because of poisoning oxidative enzymes. Myocardial metabolism requires the sampling of blood from the coronary sinus and a systemic artery to obtain arteriovenous differences of oxygen, carbon dioxide, lipoproteins, and glucose metabolites. There are more direct methods for measuring coronary blood flow in experimental animals (dog, cat, pig, monkey). The relative importance of metabolic and neurohumoral control has been evaluated in experimental animals [see reference cited by Bove (38)]. It has not been possible to reproduce coronary heart disease by exposure to tobacco smoke, which contains nicotine levels higher than ETS, so it is doubtful that existing animal models can give positive results from ETS exposure.

Nitroglycerin and organic nitrates are useful vasodilators for the relief of angina pectoris. The pharmacologic action of nitroglycerin is manifested in workers who are exposed daily to nitroglycerin and ethylene glycol dinitrate, but after a weekend of nonexposure, develop chest pain on Monday morning. Workers suffer from vasospastic angina as a result of nitrate withdrawal during the weekend and are relieved upon resuming nitrate work exposure. Autopsied workers did not show coronary arterial obstruction, confirming the occurrence of vasospastic angina brought about by weekend withdrawal from nitrate. Workers were acclimatized to the nitrate level in work environment (14–16).

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CORONARY ATHEROSCLEROSIS

The term coronary *atherosclerosis* used in this chapter refers to histopathologic changes in arteries leading to *ischemic heart disease* (see preceding section). Although both terms are included in *coronary heart disease*, there are differences in methodology. This section is devoted to progressive organic lesions of coronary arteries, the methods for detection, and their evolution, based on human observations and animal experimentation. The focus is on industrial exposure to carbon disulfide and carbon monoxide, because of the relatively greater amounts of data on these substances. The potential relevance of these industrial chemicals to ETS exposure is also discussed.

The demonstration of coronary atherosclerosis ideally should include histopathologic evidence derived from autopsy (Method D). This has been accomplished for worker exposure to carbon disulfide, which has been supported by the occurrence of hyperlipidemia in exposed workers and coronary atherosclerosis in experimental animals (Method E). On the other hand, some industrial chemicals are associated with the development of coronary atherosclerosis based on animal experiments only or on hematologic changes in workers that in animals contribute to aortic atherogenesis (see entries in Table 1). Some of these observations have been used to support the claim that ETS exposure is involved in coronary atherosclerosis. A distinction is made between concepts derived from human studies (Method D), animal experiments (Method E), and *in vitro* techniques (Method F).

Method D: Coronary Angiography and Histopathology

The most direct method for diagnosis of coronary atherosclerosis is by histopathologic examination and coronary angiogram. Although there are isolated reports that workers exposed to carbon monoxide suffer from increased coronary atherosclerosis (antemortem or postmortem), this exposure is confounded by competing risk factors such as personal habits, familial history, and environmental pollution. Among viscose rayon workers, the occurrence of coronary atherosclerosis reported at autopsy of workers dying of heart disease led to mortality studies (Method A). Workers are also reported to suffer from hyperlipidemia, which is not entirely due to carbon disulfide exposure. It is difficult to replicate earlier studies on workers using modern techniques of diagnosing coronary atherosclerosis, because exposure levels have come under strict regulation.

There are no case reports of coronary atherosclerosis in workers exposed to a single polynuclear aromatic amine because workplace exposure is to mixtures that include benzo[*a*]pyrene. Only research laboratory workers investigating benzo[*a*]pyrene are candidates for long-term exposure, and so far there has been no report of a higher incidence of heart disease. There are

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also no case reports of coronary atherosclerosis from prolonged exposure to the heavy metals and nitrogenous compounds listed in Table 1.

Method E: Coronary Atherosclerosis in Experimental Animals

Repeated attempts to induce coronary atherosclerosis in experimental animals by inhalation of cigarette smoke have failed. Additional feeding with a cholesterol-enriched diet has reportedly led to the development of atherosclerosis not involving coronary arteries. In baboons, after 2–3 years of oral feeding of cholesterol and saturated fat, and daily inhalation of cigarette smoke, arterial lesions were compared between smokers and controls. Among male baboons, the extent of carotid atherosclerosis was greater in smokers than in controls, but there were no significant differences in atherosclerosis of the aorta, coronary arteries, iliac-femoral, and bronchial arteries. Among female baboons, there were no significant differences in atherosclerosis between smokers and controls (39).

The same general remarks apply to experimental testing of carbon monoxide in levels far exceeding those reported for ETS exposure. Rabbits, pigeons, and chickens are reported to need supplementary feeding of cholesterol to show carbon monoxide-induced aortic atherosclerosis (40).

Carbon disulfide is the only industrial chemical reported to cause atherosclerosis in animals without supplemental cholesterol feeding. Coronary and aortic atherosclerosis and myocardial lesions were detected in rats after 4 months of inhalation exposure (28). There were elevations of serum cholesterol, phospholipid, and triglycerides, indicating similarity to the human form of atherosclerosis. Other investigators have tested carbon monoxide and benzo[*a*]pyrene and have not observed hyperlipidemia and atherosclerosis similar to those reported for carbon disulfide. In the past, research on carbon monoxide, benzo[*a*]pyrene, and other polynuclear aromatic hydrocarbons has not been directed to a comparison with carbon disulfide.

Polynuclear aromatic hydrocarbons have been reported to induce aortic atherosclerosis in pigeons and chickens (41–44). It has been speculated that these studies in birds relate to human subjects exposed to ETS (2). There are several reasons for the inapplicability of results of these bird experiments to coronary atherosclerosis: (a) 7,12-dimethylbenzo(*a*,*h*)anthracene and 3-methycholanthrene are not known to be present in ETS; (b) although benzo[*a*]pyrene is reportedly present in ETS, the dose administered, 50 mg/kg injection, is farfetched compared to concentration levels in SSS, which is 0.00009 mg/cigarette; (c) hepatic metabolism is essential for atherogenesis in one strain, but not in the other strain, a sequence that applies to oral or injected compounds but not to the inhalation route; and (d) the typical result is aortic atherosclerosis and rarely coronary atherosclerosis. Aortic atherosclerosis is different from coronary atherosclerosis because of myocardial extravascular support in the latter. There are intracardiac mechanisms that influence coronary circulation, which are absent in other arterial beds.

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There are long-term animal experiments designed to study carcinogenicity or polynuclear aromatic hydrocarbons and, so far, coronary atherosclerosis has not been reported in sacrificed animals.

Method F: *In Vitro* Studies of Hematologic Factors

Hematologic factors include alterations in hemoglobin oxygen transport such as carbon monoxide and methylene chloride increasing carboxyhemoglobin; and aniline and 2-toluidine leading to methemoglobinemia. The ultimate consequence is a reduced supply of oxygen and presumably atherosclerosis resulting from carbon monoxide. However, prolonged testing with methylene chloride or aniline has not been reported to produce experimental atherosclerosis, suggesting that these two industrial chemicals reduce hemoglobin oxygen transport differently from carbon monoxide.

Several techniques have been developed for the specific purpose of discovering therapeutic agents for the prevention, suppression, and reversal of atherosclerosis. Drugs for influencing blood platelets, blood lipoprotein levels, and endothelial vulnerability evolved from application of *in vitro* testing of blood derived from patients with ischemic heart disease, as well as peripheral vascular diseases. The same techniques for identifying therapeutic agents have also been applied to investigating how carbon monoxide and ETS might play a role in atherosclerosis. The interpretation of results derived from one test has been extended to include the entire progression of atherosclerosis even though the test was intended to show a therapeutic, rather than toxic, effect of chemical agents.

In vitro tests have been applied to blood from ETS-exposed subjects, based on the assumption that any reported effect will contribute to coronary atherosclerosis. It should be pointed out that chemically induced platelet aggregation leads to vascular clot formation, which does not necessarily involve interaction with endothelial cells and the formation of atherosclerotic plaque. Also, in the laboratory, it has not been possible to initiate aortic plaque formation by exceeding the normal level of fibrinogen. Any reported increase in fibrinogen level in the blood of ETS-exposed subjects may not be relevant to a potential relationship with coronary atherogenesis. It is conceivable that, for some people, ETS exposure may be perceived as stressful, with release of catecholamines, and that catecholamines are responsible for *in vitro* testing results. It has not been possible to conduct a double-blind testing of ETS exposure since both investigator and subject can detect ETS presence.

Platelet Aggregation

Exposure of healthy nonsmokers to ETS is alleged to alter results of *in vitro* testing of platelets in platelet-rich plasma. Aggregation of platelets is

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tested by the following agents added *in vitro*: edetic acid and formaldehyde or prostaglandin. The possibility that ETS exposure increases platelet aggregation is alleged to be an important step in the evolution of coronary atherosclerosis in nonsmokers (2).

In vitro studies of platelet aggregation in blood derived from smokers have reported inconsistent results, which question the applicability of this method to ETS exposure in nonsmokers. Platelet aggregation testing using whole blood reported no statistically significant differences between nonsmokers and smokers (45). Cigarette smoking is reportedly associated with alterations in platelet factors involved in thrombus formation, but the change has been attributed to the presence of carbon monoxide levels higher than those reported in subjects exposed to ETS (46). *In vitro* testing does not necessarily reflect events *in vivo*. Although platelets may be activated *in vivo*, they become attached to erythrocytes or form platelet aggregates during the collection and centrifugation needed to make platelet-rich plasma. There is some evidence that activated platelets are lost from supernatant "platelet-rich plasma," which includes older or less active platelets.

Plasma Fibrinogen Levels

Another *in vitro* test for a clotting factor has been added to the list of reports supporting the ETS–heart disease hypothesis. Patients with ischemic heart disease were questioned about their smoking habits, and nonsmokers were queried for ETS exposure in the workplace and household. Control subjects were derived from the same community in Australia (47). It was reported that the collected blood samples showed higher fibrinogen concentrations among current smokers than nonsmokers. Subjects exposed to ETS had higher levels than those not exposed. The differences were not statistically significant because of the high variability of measured fibrinogen levels. According to the questionnaire responses, levels of ETS exposure at work were reported to be higher than at home, but the estimated odds ratio for heart disease was less than one. The investigators interpreted their results to indicate inaccurate reporting of ETS exposure or the possibility that household exposure to ETS is associated more with heart disease than is workplace exposure. The potential relevance of fibrinogen levels in relation to ETS exposure is further questioned by observations that psychosocial factors may influence the plasma fibrinogen concentration in patients with ischemic heart disease (48).

CARDIAC ARRHYTHMIA AND MYOPATHY

The third and last group of methods for establishing cardiac toxicologic profiles for industrial chemicals relates to alterations in cardiac function.

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The methods are intended to detect irregularities in heart beat or rhythm, to measure excitability of the intact heart, and to record electrical properties of excised atrium and papillary muscle. Cardiac output is measured by the tracer dilution technique and ventricular imaging in patients; invasive procedures are required for application of the Fick principle in patients and insertion of blood flow recorders in experimental animals. Perfusion of the excised heart offers an opportunity of measuring myocardial contractility and metabolism. Enzymatic studies and electron microscopy complete the techniques for detecting cardiomyopathy. All these procedures have been applied to determine the occurrence and mechanism for two groups of diseases: irregular heart beat or arrhythmia, and cardiomyopathy.

Method G: Irregular Heart Beat

Industrial chemical poisoning can be manifested by irregularities of heart beat or cardiac arrhythmia, in the order of increasing severity: ranging from tachycardia or bradycardia, atrioventricular block, atrial or ventricular extrasystole, atrial fibrillation, to ventricular fibrillation and cardiac arrest. The benign forms (up to atrial fibrillation) are reversible by stopping chemical exposure, but ventricular fibrillation and cardiac arrest require heroic efforts. Poisonings characterized by cardiac arrhythmias have been reported for the following (see Table 1, Method G): most halogenated and nonhalogenated solvents, some nitrogenous compounds, one heavy metal (lead), and one oxide (carbon monoxide). The arrhythmia results from a direct action of the chemical on the heart, specifically by altering excitability, conduction, and refractoriness of one or more of the following: atrial muscle, atrioventricular node, conducting system, and ventricular muscle. The effects have been reported in appropriate human studies and animal experimentation. The occurrence of poisoning by industrial chemicals does not support the proposition that since the same chemicals may be reported at minute levels in ETS, then ETS also may lead to the development of heart disease in workers.

Method H: Experimentally Induced Cardiomyopathy

The most extreme example of unjustified application of results from animal experiments to ETS exposure of nonsmokers is as follows: in the course of attempting to determine whether long-term cigarette smoking leads to cardiomyopathy, rabbits were exposed in an infant incubator (49). It was reported that all the smoke from three burning cigarettes entered the inlet of the incubator through a mechanical device and rabbits were kept for 30 min. This description appears to this author as a sealed chamber with cigarette smoke entering the inlet for 30-min periods. Several groups of rabbits were

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sacrificed: controls, after one 30-min exposure, twice daily exposure for 2 weeks, and twice daily exposure for 8 weeks. The heart was studied for mitochondrial oxidative processes. There was a decrease in respiration as well as in phosphorylation rate that was interpreted by the investigators as cardiomyopathy. The investigators recognized that carbon monoxide in the incubator was probably responsible for metabolic changes but they did not moniton air or blood levels.

Hugod and collaborators (50–52) exposed rabbits to one of the following mixtures: carbon monoxide 220 mg/m^3 or four times TLV; carbonyl sulfide 130 mg/m^3 or five times TLV; nitric oxide 6 mg/m^3 or one-fifth the TLV. The rabbits were in air-tight exposure chambers containing freely flowing air or predetermined mixtures in air for periods ranging from 1 to 7 weeks. The results of 140 rabbits sacrificed for electron microscopic examination performed blindly showed no morphological signs of myocardial damage. The four vapor constituents, in levels far exceeding ETS levels, were not associated with ultrastructural changes in rabbit heart, signifying the absence of cardiomyopathy.

The rabbit exposure studies described above were extended to include biochemical and histomorphologic investigation of atherosclerosis. Exposure to each of the four gas–air mixtures was not related to intimal damage of the aorta and coronary arteries. The negative results noted for carbonyl sulfide exposed rabbits do not support the claim that this known metabolite for carbon disulfide is responsible for coronary atherosclerosis reported by other investigators.

Cardiomyopathy has been reported following exposure to halogenated solvents, based on case reports of poisoning and experimental studies on intact and perfused heart. Cardiomyopathy from heavy metals is described in case reports of individuals drinking beer from containers that leached arsenic, cadmium, or lead (16). Cardiomyopathy from hydrocyanic acid is also based on case reports of poisoning and is readily supported by biochemical studies of heart muscle. Carbon monoxide is probably the most frequently encountered industrial and household chemical associated with death by cardiomyopathy. History of exposure to vehicular emissions or household natural gas is verifiable by blood analysis for carboxyhemoglobin. Among nonhalogenated solvents, only phenol has been reportedly related to cardiomyopathy (16).

CONCLUDING REMARKS

Among more than 32 industrial chemicals potentially related to heart disease, only four substances or chemical classes have extensive supportive evidence: carbon monoxide, carbon disulfide, ethylene glycol dinitrate and organic nitrates, and methylene chloride and halogenated solvents. The ef-

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fects of other industrial chemicals (oxides, nonhalogenated solvents, nitrogenous compounds, and heavy metals) have not been adequately supported by human studies and animal experiments.

Methylene chloride is a solvent prototype for industrial chemicals that may be related to cardiac arrhythmia and myopathy in lethal or sublethal levels. Carbon disulfide is a selected prototype for industrial chemicals that may be related to ischemic heart disease or coronary atherosclerosis. There are no data indicating whether prolonged exposure to low levels of methylene chloride is associated with ischemic heart disease or whether high levels of carbon disulfide are associated with cardiac arrhythmia and myopathy. Methods to establish a cardiac toxicologic profile applied to one prototype need to be applied to the other.

The cardiac toxicologic profile for carbon disulfide is as follows: (A) mortality studies of viscose rayon workers report excess ischemic heart disease deaths, provided predisposing or other risk factors are present; (B) there is a high incidence of angina pectoris reported in workers exposed to carbon disulfide; (C) there is a reduction in coronary blood flow reported in workers developing ischemic heart disease, but there are no published results of myocardial tracer clearance studies; (D) coronary angiogram and postmortem histopathologic studies report coronary atherosclerosis associated with carbon disulfide exposure; (E) coronary atherosclerosis developed in experimental animals exposed to carbon disulfide, with or without dietary cholesterol supplement. There is no information for (F) *in vitro* hematologic factors and (G) cardiac arrhythmia; (H) experimental cardiomyopathy was reportedly not detected by electron microscopy in animals exposed to five times TLV for carbon disulfide.

The cardiac toxicologic profiles for carbon disulfide and ETS are compared in Table 3. There are no comparative studies on workers with and without ETS exposures. The theory that ETS causes ischemic heart disease is based on inferences from the following: (A) epidemiologic studies of household exposures reported for nonsmoking spouses of smokers; (B) exercise studies of anginal patients with ETS exposure, but questionable protocol; (C) coronary blood flow assumed to be insufficient because carbon monoxide present in ETS; (D) coronary atherosclerosis assumed to occur because aortic atherosclerosis reported in animals exposed to carbon monoxide at considerably higher levels than ETS; (E) coronary atherosclerosis supposedly occurs because benzo[*a*]pyrene reportedly associated with atherosclerosis in cholesterol-fed birds; (F) *in vitro* testing for platelet aggregation and reduced fibrinogen level, suggesting atheromatous plaque formation; (G) cardiac arrhythmia postulated based on ventricular excitability studies of animals exposed to carbon monoxide; and (H) cardiomyopathy inferred from rabbit heart mitochondrial studies.

It is the opinion of this author that the available studies do not support a judgment that ETS exposure is associated with any form of occupation-re-

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TABLE 3. *Cardiac toxicologic profile for carbon disulfide and environmental tobacco smoke*

Method	Carbon disulfide	Environmental tobacco smoke (ETS)
Ischemic heart disease		
A. Mortality studies	Excess ischemic heart disease deaths among rayon viscose workers provided predisposing factors present	No information on workers exposed to ETS
B. Exercise testing and angina pectoris	Higher incidence of angina in rayon viscose workers; exercise testing protocol must meet U.S. agency standards	Anginal patients have shorter time to pain onset when exposed to ETS; cigarette smoking questionable risk factor in angina patients
C. Coronary blood flow indicators	Reduced coronary blood flow in patients with ischemic heart disease	
Coronary atherosclerosis		
D. Coronary angiography and histopathology		
E. Atherosclerosis in experimental animals	Coronary atherosclerosis in rats without cholesterol feeding	Polynuclear aromatic amines causing aortic atherosclerosis in cholesterol-fed birds
F. *In vitro* hematologic factors	No information	Platelet aggregation, endothelial cell damage and reduced fibrinogen level
Cardiac arrythmia and myopathy		
G. Irregular heart beat	No information	Ventricle excitability studies of animals exposed to carbon monoxide
H. Experimentally induced cardiomyopathy	No ultrastructural changes in rabbit heart	Heart mitochondria studies from rabbits exposed to ETS

lated heart disease. Although ETS reportedly contains constituents that have been associated with occupational heart disease, the concentrations are so low that it is unlikely for any substance to attain the corresponding TLV in a work environment.

Carbon disulfide can be used as a reference model for testing whether an industrial chemical can be considered as an etiologic factor in ischemic heart disease and coronary atherosclerosis. The most comprehensive and critical review of carbon disulfide has been written by members of the Chemical Industry Institute of Toxicology. The theory that ETS exposure causes heart disease was recently summarized by university scientists who have dismissed valid criticisms as industry-supported. All research results, including industry-funded sources, should be used in evaluating the role of ETS in heart disease.

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